Remarks

Claims 1, 2, 4-6, 8, 11-13, and 16 were pending in the subject application. By this Amendment, claims 1 and 6 have been amended and claim 16 has been cancelled. The undersigned avers that no new matter is introduced by this Amendment. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Claims 8 and 11-13 remain pending but withdrawn from consideration. Accordingly, claims 1, 2, 4-6, 8, and 11-13 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Applicants acknowledge that claims 8 and 11-13 have been withdrawn from further consideration as being drawn to a non-elected invention. However, Applicants wish to reserve the right to request rejoinder of the non-elected process claims upon an indication of an allowable product claim in accordance with MPEP §821.04.

By this Amendment, claim 1 has been amended to recite that the human Müller cells are adult human Müller cells. Support for this amendment can be found, for example, at page 4, lines 29-32, and page 5, lines 11-13 and 22-25, and the claims as originally filed.

Claims 1, 4, and 5 are rejected under 35 USC §102(b) as anticipated by Kelley *et al.* (*Opthalmol Vis Sci*, 1995, 36:1280-1289). The Examiner asserts that the Kelley *et al.* publication expressly or inherently discloses each element of the claims. Applicants respectfully traverse.

The method of claim 1 as currently amended uses cells obtained from the adult human retina, which express markers of mature Müller cells: "obtaining one or more adult human Müller cells expressing markers of mature Müller cells." In contrast, the cells disclosed by Kelley *et al* are isolated from fetal retina, and therefore do not express markers of mature Müller cells. As such, the cells used in the method of the invention are distinct from those disclosed in the Kelley *et al.* publication.

Kelley *et al.* refer to fetal human retinal progenitors; at no point do they identify Müller glia with mature markers as the source of neurons. The authors of the publication characterize the cell types derived from their cultures as immunoreactive for neuron-specific enolase, (indicating that they

are neurons), which they believed were either retinal ganglion cells or amacrine cells (see page 1282, second column, first complete paragraph). Kelley *et al.* describe proliferating cells as "flattened cells, which were probably progenitor cells or Müller cells"; however, they did not attempt to specifically characterize Müller glia with stem cell characteristics in their cultures. Furthermore, the Kelley *et al.* publication does not demonstrate that the cells they isolated were immortal, which is a characteristic of stem cells. Although the Kelley *et al.* publication demonstrates that growth factors can stimulate the proliferation of "foetal retinal progenitors", it does not demonstrate that adult human retina harbor a population of Müller glia that exhibit mature Müller glial markers and stem cell characteristics, as required by the present claims. Kelley *et al.* did not derive Müller cell lines that could be grown indefinitely, *in vitro,* for use in cell-based therapies, which is the subject of the present invention.

It is well settled that, to be anticipatory under 35 U.S.C. §102(b), a single prior art reference must disclose each and every element as set forth in the claim, either expressly or inherently. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631; 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). As the Kelley *et al.* publication does not disclose obtaining the Müller cells as recited in the claims, Applicants respectfully submit that the reference does not anticipate the claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §102(b) is respectfully requested.

Claim 6 is rejected under 35 USC §102(b) as anticipated by, or in the alternative, under 35 USC §103(a) as obvious over Kelley *et al.* (*Opthalmol Vis Sci*, 1995, 36:1280-1289). The Examiner acknowledges that the human retinal progenitor cell composition of Kelley *et al.* is not produced by the same methods as that of the subject application; however, the Examiner asserts that the composition taught by Kelley *et al.* is not distinguishable from that of the claimed invention. Applicants respectfully traverse.

Applicants' remarks in response to the rejection of claims 1, 4, and 5 based on the Kelley *et al.* publication are incorporated herein by reference. The method recited in claim 6 uses cells obtained from the adult human retina that express markers of mature Müller cells. In contrast, the cells disclosed by Kelley *et al* are isolated from fetal retina, and therefore do not express markers of mature Müller cells. As such, the cells used in the method of the invention are distinct from those

disclosed in the Kelley *et al.* publication. Kelley *et al.* refer to fetal human retinal progenitors; at no point do they identify Müller glia with mature markers as the source of neurons.

Applicants respectfully submit that the presence of inherent matter must be grounded on more than speculation, it must be a certainty. *Ethyl Molded Product Co. v. Betts Package Inc.*, 9 USPQ 2d 1001, 1032-1033 (I.D.KY 1988) ("the doctrine of inherency is available only when the prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation" (emphasis added)).Furthermore, when the reference is silent about the asserted inherent characteristic, while such a gap in the reference may be filled with recourse to extrinsic evidence, the extrinsic evidence

> must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 49 USPQ 2d 1949, 1950-1951 (Fed. Cir. 1999).

It is true that the patentability of a claimed product (*e.g.*, a cell) does not depend on its method of production (*e.g.*, isolation method and/or culture conditions) per se. However, when assessing the patentability of the claims over the prior art, the Examiner is required to consider any structural distinctions that are implied by the steps in the method of production. Thus, the fact that the de-differentiated Müller cells of the invention were obtained from a different source (adult human Müller cells) and cultured according to a different process than the cells of the cited reference must be considered in determining whether the cells in question represent the same cell having the same characteristics, particularly when the cited reference is silent as to the characteristic recited in the claim.

Applicants note that no rationale is provided in the Office Action for the alternative rejection under 35 USC §103(a). The key to supporting any rejection under 35 U.S.C. §103(a) is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398; 82 USPQ2d 1385 (2007) noted that the analysis supporting a rejection under 35 U.S.C. §103(a) should be made explicit. There must be

some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. MPEP §2142.

Accordingly, reconsideration and withdrawal of the rejections under 35 USC §102(b) and 35 USC §103(a) is respectfully requested.

Claim 6 is rejected under 35 USC §102(b) as anticipated by, or in the alternative, under 35 USC §103(a) as obvious over Walcott *et al.* (*Clinical Expert Opthal,* 2003, 31:246-249). The Examiner acknowledges that the composition of Walcott *et al.* publication (a human fetal retinal progenitor cell composition) is not produced by the same methods as that of the subject application; however, the Examiner asserts that the composition taught by Walcott *et al.* is not distinguishable from that of the claimed invention.

The cells disclosed by Walcott *et al.* are not the same as those used in the composition of claim 6. The study described in the publication by Walcott *et al.* indicates that Müller cells in the "foetal human retina" express the progenitor cell marker nestin *'in situ'*. However, there is no disclosure in this publication of the authors attempting to isolate the cells, culture or expand them *in vitro*, or differentiate them into neurons for use in therapy. Moreover, this publication does not show the existence of these cells in the adult human retina.

In the final sentence of Walcott *et al.,* the authors suggest that "[i]dentification of the factors regulating nestin expression by adult Müller cells *in vitro* could provide a basis for reestablishing retinal cell proliferation… [which] may prove valuable in development of transplantation procedures… ". From this statement it is reasonable to conclude that the authors did not identify nestin-positive cells in the adult human retina and for this reason they suggested that by inducing expression of nestin in the adult cells *in vitro,* it would be possible to make them proliferate as a source of cells for transplantation. As indicated above, when assessing the patentability of the claims over the prior art, the Examiner is required to consider any structural distinctions that are implied by the steps in the method of production. Thus, the fact that the de-differentiated Müller cells of the invention were obtained from a different source (adult human Müller cells) and cultured according to a different process than the cells of Walcott *et al.* must be considered in determining whether the cells in question represent the same cell having the same characteristics, particularly when the cited reference is silent as to the characteristic recited in the claim.

The Office Action does not provide a rationale for the alternative rejection under 35 USC §103(a). As indicated above, the key to supporting any rejection under 35 U.S.C. §103(a) is the clear articulation of the reason(s) why the claimed invention would have been obvious. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. MPEP §2142.

Accordingly, reconsideration and withdrawal of the rejections under 35 USC §102(b) and 35 USC §103(a) is respectfully requested.

Claims 1, 2, and 16 are rejected under 35 USC §103(a) as obvious over Limb *et al.* (*Investig Opthal & Visual Sci,* 2002, 43:864-869), in view of Kelley *et al.* (*Opthalmol Vis Sci*, 1995, 36:1280-1289). The Examiner asserts that it would have been obvious for one of ordinary skill in the art to culture Müller cells as taught by Limb *et al.* and Kelley *et al.* on Matrigel or fibronectin matrix in the presence of EGF to determine the effect of this cell culture on cell morphology. Applicants respectfully traverse.

Applicants' remarks in response to the rejection of claims 1, 4, and 5 based on the Kelley *et al.* publication are incorporated herein by reference. The method of claim 1 uses cells obtained from the adult human retina that express markers of mature Müller cells. In contrast, the cells disclosed by Kelley *et al* are isolated from fetal retina, and therefore do not express markers of mature Müller cells. As such, the cells used in the method of the invention are distinct from those disclosed in the Kelley *et al.* publication.

The Limb *et al.* publication is co-authored by the present inventors and is an article describing the first characterization of a spontaneously immortalized Müller cell line. When this article was published, it was not known that the cells of the cell line were stem cells; this was established subsequently, following further studies. Because the nature of the cells of the invention is not disclosed in either of the cited references, it is not possible for one of ordinary skill in the art to arrive at the present claims based upon their teachings. There would have been no motivation for one of ordinary skill in the art to combine the teachings of the Kelley *et al.* publication and the Limb *et al.* publication in such a way to obtain the adult human Müller cells and culture them to induce dedifferentiation into a progenitor phenotype as recited in claim 1. Obviousness cannot be predicated

on what is not known at the time an invention is made. MPEP §2141.02. As such, the claimed invention is not obvious in view of the cited references.

Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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